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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/829,113	04/09/2001	William Edward Evans	44158/209598 (5853-3)	2302

29312 7590 11/24/2003

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/829,113	EVANS ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1634	

-- Th MAILING DATE of this communication appears on th cover sh t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-16, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel et al (Nucleic Acids Research (1991) 19:3561-3567) and further in view of Michalatos-Beloin et al (Nucleic Acids Res. (1996) 24:4841-4843).

Li teaches a method of determining the haplotype structure of a contiguous DNA segment comprising a first nucleotide polymorphism and a second nucleotide polymorphism (see page 360, figure 1) comprising:

(a) obtaining a DNA sample from a human source comprising said contiguous DNA segment (page 358, column 1),

(b) using said DNA sample as a template for polymerase chain reaction amplification of a DNA fragment to form a product which is capable of being subject to intramolecular ligation (page 358, column 2, subheadings "GPA-specific PCR" and page 360, figure 1),

wherein the PCR amplification is performed with

(i) a first primer capable of annealing to a region adjacent to the first NP and distal to the second NPs (see figure 1, where the MN-FP primer is adjacent to the 5'G/T polymorphism and distal from the 3' G/T, C/A/G and C/T polymorphisms)

(ii) a second primer capable of annealing to a region adjacent to the second NP and distal to the first NP (see figure 1, where the MN-CR primer is adjacent to the 3' G/T, C/A/G and C/T polymorphisms and distal from the 5' G/T polymorphism),

(c) ligating the ends of the DNA fragment to each other so as to produce a circular DNA molecule (page 358, subheading "ligation of the amplified fragment" and page 360, figure 1), wherein the ligation brings the first and second polymorphisms into closer proximity on the circular DNA molecule (see figure 1, page 360 and page 361, column 1, which states "ASIP rather than nested PCR, can be applied to haplotyping of polymorphisms separated by a distance that is too long to be amplified by PCR"),

(d) determining the haplotype of the first and second nucleotide polymorphism by allele specific inverse PCR amplification (page 358, subheading "Allele specific PCR" and page 360, figure 1).

With regard to claims 5-8, Li teaches first, second and third NPs that are single nucleotide substitutions with some NPs located between the end NPs whose haplotype is determined (see figure 1, page 360).

With regard to claim 9, Li teaches use of human sources (see page 358, column 1).

With regard to claim 13, Li teaches that the primers are allele specific (see page 360, figure 1).

With regard to claims 14-16, Li teaches determination of each allele of the clinically relevant Glycophorin gene (see page 358, column 1 and page 360, figure 1).

With regard to claims 21 and 22, Li teaches a DNA sequence immediately adjacent to the 5' and 3' NPs which is less than 50 bases long.

Li suggests the use of the method on haplotyping distances that are too long to be PCR amplified (see page 361, column 1).

While Li suggests applying the method to situations with polymorphisms that are distant from one another, Li does not exemplify application of the method to sequences which are 200 to 30,000 bases apart nor the use of long range PCR.

Regarding claim 1 and dependent claims 2-4, Patel teaches that inverse PCR methods such as those used by Li can be applied to haplotype sequences up to 10 kb apart and suggests that even larger regions can be used (page 3567, column 1, lines 6-9).

Regarding claims 11 and 12, Patel teaches restriction digestion to enhance inverse PCR and detection with such digestion (see page 3562, column 1 and page 3563, figure 2)

Patel teaches mutations which are substitutions of single nucleotides and where there are a series of nucleotide polymorpisms located between the two amplified polymorphisms (see page 3561, column 2 and page 3562, figure 1). Patel teaches determing the presence of multiple different polymorphisms (see page 3565, column 1, subheading "Double ARMS Inverse PCR (DARMSI-PCR)". Patel teaches amplification and detection of each haplotype in the same gene, the globin cluster (page 3562, figure 1). Patel further teaches that the method can be used for diagnostic purposes (see page 3567, column 1).

Michalatos-Beloin teaches haplotyping methods where the molecules are prepared by long range PCR (page 4842, figures 2 and 3). Michalatos-Beloin also teaches that amplification of up to 40 kb should be possible (see page 4843 (listed as page 4867), column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the long range PCR method of Michalatos-Beloin to amplify the sample of Li since Michalatos-Beloin states "The allele-specific long range PCR products were used as templates for amplification of the STR (page 4867, column 1)". An ordinary practitioner would have been motivated to use long range PCR to prepare the template for the method of Li in order to extend the range of detection of polymorphisms in order to solve the problem of Li that there are "polymorphisms

separated by a distance that is too long to be amplified by PCR (see page 361, column 1)." Li recognizes the problem in that some haplotypes are too distant to be amplified by standard PCR. Michalatos-Beloin solves the problem using long range PCR. Further, Michalatos-Beloin notes "The ability to isolate hemizygous DNA segments readily from heterozygous genomes via molecular haplotyping will provide the accuracy necessary in these diverse applications (page 4867, column 2). Thus, application of the method of Michalatos-Beloin to the inverse PCR method of Li can be used to increase the accuracy of the Li method. Further motivation to apply the Michalatos-Beloin method to Li is provided by Patel, who teaches that haplotyping using inverse PCR is desirable on long segments, even haplotypes separated by more than 10,000 nucleotides (see page 3567, column 1). This represents further motivation to apply the method of Li to more widely separated polymorphisms, as well as teachings on how to perform that method.

4. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel et al (Nucleic Acids Research (1991) 19:3561-3567) in view of Michalatos-Beloin et al (Nucleic Acids Res. (1996) 24:4841-4843) as applied to claims 1-16, 21 and 22 and further in view of Krynetski et al (Proc. Natl. Acad. Sci. (1995) 92:949-953).

Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin teach the limitations of claims 1-16, 21 and 22 as discussed above. Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin do not teach application of the method to the TPMT gene.

Krynetski teaches that there are two haplotypes in the TPMT gene, one of which is associated with cytotoxicity in chemotherapeutic treatment using methylmercaptopurine (see page 949, columns 1 and 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin to haplotype the TPMT gene since Krynetski teaches "Identification of the inactivating mutations at the TPMT locus would not only provide important insights into the molecular mechanisms of this genetic polymorphism but might also offer a method of prospectively identifying heterozygotes and TPMT-deficient patients prior to treatment with potentially toxic dosages of mercaptopurine (page 949, column 2)". Thus, an ordinary practitioner would have been motivated to haplotype the TPMT gene using the method of Patel in view of Michalatos-Beloin, where Patel teaches that the method is useful "for routine diagnostic purposes (page 3567, column 1)", in order to diagnose patients who are TPMT deficient prior to toxic treatment.

5. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel et al (Nucleic Acids Research (1991) 19:3561-3567) in view of Michalatos-Beloin et al (Nucleic Acids Res. (1996) 24:4841-4843) as applied to claims 1-16, 21 and 22 and further in view of Martin et al (Am. J. Hum. Genet. (2000) 67:383-394).

Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin teach the limitations of claims 1-16, 21 and 22 as discussed above.

Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin do not teach application of the method to the listed genes.

Martin teaches haplotype analysis of the ApoE gene in order to analyze the presence of Alzheimer's disease (abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin to haplotype the ApoE gene since Martini teaches "Haplotype analysis using family data increased significance over that see in single-locus tests for some of the markers, and for these data, improved localization of the gene (abstract)." Thus, an ordinary practitioner would have been motivated to haplotype the ApoE gene using the method of Patel in view of Michalatos-Beloin, where Patel teaches that the method is useful "for routine diagnostic purposes (page 3567, column 1)", in order to diagnose patients who are at risk for Alzheimer's disease.

Response to Arguments

6. Applicant's arguments filed October 6, 2003 have been fully considered but they are not persuasive.

Applicant first sets out the ordinary standards relating to the obviousness analysis and discusses the references.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention

where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Applicant attempts to denigrate the statement by Li that the ASIP method is one way to achieve haplotyping of polymorphisms that are too long to be amplified by PCR. Applicant argues that the more plausible interpretation is that Li relates to a situation in which even long range PCR cannot be used. This is not found persuasive because if, as Applicant correctly notes, long range PCR is taken as known to Li, the Li could easily have said something like too long to be amplified by long range PCR. However, Li did not make that statement, but only stated that regular PCR was insufficient. This reading is supported by an analysis of the actual methodology of Li, in which Li performs both PCRs, the GPA specific PCR prior to ligation, and the allele specific PCR after ligation, with Taq polymerase or Amplitaq gold polymerase, neither of which is used along in long range PCR. So when Li discusses PCR in the materials and methods, Li is discussing ordinary, not long range, PCR. Consequently, the proper interpretation of Li's final comment is that ordinary PCR is inadequate, and Li is not referring to long range PCR. Therefore, the statement by Li provides a problem which is solved by the long range PCR method of Michalatos-Beloin who teaches the use of long range PCR in haplotype analysis.

Applicant then argues that the quote is taken out of context because Li is using physically close nucleotides which do not bring the polymorphisms closer together.

First, as figure 1 shows, the polymorphisms are closer together in one direction than they previously were. Second, while Li exemplifies the method with a particular target, Li is clearly intent on providing a general method for haplotype analysis. This is expressly indicated by Li, who states that this can be applied to other polymorphisms at page 53 that are separated by distances too far apart for standard PCR. So even if Li does not exemplify bringing polymorphisms closer together, Li expressly teaches and suggests such a course, and expressly teaches separation that is too far apart for standard PCR. Since Standard PCR can easily amplify 1000 or more bases, Li is discussing polymorphisms that are at least that distant, and which necessarily meet the limitation argued by Applicant.

Applicant then argues that there is no specific finding to support the problem in haplotyping sequences more than 200 base pairs apart. This is simply incorrect. Li expressly states the issue, noting that some polymorphisms are too far apart to be amplified by PCR. This is a specific finding of the problem, stated by Li.

Applicant then argues hindsight reasoning is used. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant then conducts a piecemeal examination of the references, picking apart Michaelos-Beloin by noting that this reference is complete in itself and that there is no motivation to combine the references. In every obviousness rejection, the references necessarily function prior to combination, or else they could not be published. So the question is not whether the methods work, but whether the combination is sufficiently prima facie obvious based upon the analysis of the Graham v John Deere factors. In the current case, there is a specific problem which is recognized by Li, and for which a solution is provided by Patel and Michaelos-Beloin. These references provide the teachings and motivations which render the claimed invention obvious.

Applicant then argues the rejection of claim 21 by stating that it is misleading to read the second PCR of Li to the first step of claim 21. Here Applicant reads a limitation into the claim that is not currently present. The claim simply requires annealing sites which are present in every DNA sequence at every position. The claim does not require any particular primers to be used or made. So Applicant's entire argument in this section is based upon an incorrect and overly narrow reading of the claims. Claim 21 states that the DNA segment comprises "a DNA sequence immediately 5' to the first NP that encompasses an annealing site for a primer." In fact, the sequence immediately

adjacent to any of the polymorphisms of Li are capable of functioning as annealing sites for primers and meet this limitation. So Applicant's argument is not drawn to the actual claim limitation and is not persuasive.

Applicant relies upon overcoming the base rejections to overcoming the rejections of claims 17 and 18. Since the base rejections are maintained, so are these rejections.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is currently 703-308-6568. In mid January, 2004, when TC 1600 relocates to the new USPTO facility in Alexandria, the examiner's phone number will become 571-272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The supervisor's new telephone number in mid January will be 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is currently 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634